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#114

NONPRECEDENTIAL

Paper No. 110

UNITED STATES PATENT AND TRADEMARK OFFICE

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PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

IAN **GARNER**,
MICHAEL L. DALRYMPLE, DONNA E. PRUNKARD,
and DONALD C. FOSTER
(5,639,940),

Junior Party,

v.

WILLIAM H. **VELANDER**,
WILLIAM N. DROHAN, HENRYK LUBOŃ,
and JOHN L. JOHNSON (DECEASED)
(08/443,184),

Senior Party.

Interference No. 104,242

Before McKELVEY, Senior Administrative Patent Judge, and SCHAFER and TORCZON, Administrative Patent Judges.

TORCZON, Administrative Patent Judge.

DECISION ON MOTIONS

(PURSUANT TO 37 CFR § 1.640)

A. INTRODUCTION

1. Both parties have filed seven preliminary motions. Velander also has a pending motion to strike. Garner's motion on inventorship has been deferred until the priority phase (Paper No. 101).

2. Garner preliminary motion 1 seeks to add Garner's 09/232,488 reissue application.

3. Garner preliminary motion 2 seeks judgment that Velander's involved claims are unpatentable.

4. Garner preliminary motion 3 seeks substitution of a new count, contingent on the granting of Garner preliminary motion 2.

5. Garner preliminary motion 4 seeks substitution of two new counts, contingent upon the denial of Garner preliminary motion 2.

6. Garner preliminary motion 7 seeks to add claims to Garner's reissue application, contingent on the granting of Garner preliminary motions 1 and 4.

7. Garner preliminary motion 5 seeks substitution of a new count, contingent on the denial of Garner preliminary motion 4.

8. Garner preliminary motion 6 seeks to add claims to Velander's involved application.

9. Velander preliminary motion 1 seeks to add claims to Velander's involved application and to be accorded benefit of a Velander application.

10. Velander preliminary motions 2 and 5 seek to add claims to Velander's involved application and to be accorded benefit of a Velander application, respectively, contingent on the granting of Garner preliminary motion 3.

11. Velander preliminary motions 3 and 6 seek to add claims to Velander's involved application and to be accorded benefit of a Velander application, respectively, contingent on the granting of Garner preliminary motion 4.

12. Velander preliminary motions 4 and 7 seek to add claims to Velander's involved application and to be accorded benefit of a Velander application, respectively, contingent on the granting of Garner preliminary motion 5.

B. BACKGROUND

1. The subject matter of this interference relates generally to producing mammals, particularly livestock, that have been genetically altered ("transgenic animals") to produce a particular protein of pharmacological interest–fibrinogen–that can be recovered from the milk of the mammal.

2. Fibrinogen consists of two copies of three separate peptides: the Aα chain, the Bβ chain, and the γ chain (Paper No. 22 (Garner Mot. 2) at 6, ¶9 (uncontested)).

3. Fibrinogen polypeptides need additional processing ("post-translational modification") before they are biologically active (Paper No. 22 at 6, ¶9).

4. The fibrinogen deoxyribonucleic acid (DNA) sequences would need to be associated with regulatory sequences and secretion signals to ensure that they are expressed with milk proteins and that they are secreted into the host mammal's milk.

Garner's patent

5. The involved 5,639,940 ("940") patent issued to Garner et al. ("Garner") on 17 June 1997.

6. The 940 patent issued from Garner's 08/206,176 application, filed 3 March 1994.

7. Garner was not accorded the benefit of any earlier application.

Velander's application

8. The involved 08/443,184 ("184") application of Velander et al. ("Velander") was filed 17 May 1995.

9. Velander was accorded the benefit of its 08/198,068 ("068") application, filed 18 February 1994.

The count

10. The count, which is based on Garner's claims 18 and 21 and on Velander's claims 66 and 69, reads as follows:

A method for producing biocompetent fibrinogen comprising:

providing a transgenic female non-human mammal carrying in its germline heterologous DNA segments encoding Aα, Bβ, and γ chains of fibrinogen, wherein said segments are expressed in a mammary gland of said mammal and biocompetent fibrinogen encoded by said segments is secreted into milk of said mammal;

collecting milk from said mammal; and

recovering said biocompetent fibrinogen from said milk.

OR

A transgenic non-human female mammal that produces recoverable amounts of biocompetent human fibrinogen in its milk, wherein said mammal comprises:

a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain,

a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bβ chain, and

a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen γ chain, and

further wherein each chain is derived from the same species and is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal.

OR

A non-human mammal carrying in its germline DNA segments encoding Aα, Bβ, and γ chains of fibrinogen, wherein female progeny of said mammal express said DNA segments in a mammary gland to produce biocompetent fibrinogen.

11. All of Garner's claims (1-33) correspond to the count.

12. All of Velander's allowed claims (64-73) correspond to the count.

C. GARNER'S PRELIMINARY MOTIONS

1. Preliminary motion 2 (Paper No. 21)

a. Garner moves to have Velander's claims 64-73 held unpatentable under 35 U.S.C. §§ 102(b) and 103 (at 2). Since Garner has not identified a single reference that anticipates all of the limitations of any given claim, we understand the argument to be that the subject matter of Velander's claims was unpatentable under § 103 in view of § 102(b) prior art.

b. Garner concedes that, if this motion is granted, then Garner's 940 patent claims are likewise unpatentable (Paper No. 22 at 16 n.*).

c. Garner has provided reasons why it believes each of the Velander involved claims should be found to be unpatentable.

d. In opposing Garner preliminary motion 2, Velander does not argue that its claims are separately patentable (Paper No. 41 (Velander Opp. 2)). Consequently, we will analyze the patentability of all of the claims in view of representative[1] claim 65:

> A transgenic non-human female mammal that produces recoverable amounts of biologically active human fibrinogen that is converted to fibrin upon reaction with human thrombin in its milk, wherein said mammal comprises:
>
> a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain,
>
> a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bβ chain, and
>
> a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen γ chain, and
>
> further wherein each chain is derived from the same species and is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal.

e. Claim 65 is not limited to the use of either genomic DNA or cDNA. For the purposes of this decision, genomic DNA will be distinguished from cDNA by the presence or absence, respectively, of introns.[2]

f. Claim 65 is not limited to production of any particular amount of biologically active human fibrinogen, provided the produced amount is "recoverable". Accord, Paper No. 41 at 4. Neither party has pointed to a definition of recoverable in Velander's disclosure. In a response to an office action, Garner provided the following definition (VX29 at 9):

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[1] Velander does not contest Garner's material fact stating that Velander claims 64 or 65 are representative (Paper No. 22 at 4, ¶3).

[2] Portions of the gene that do not encode the protein and which are not present in cDNA.

> "Recoverable" is used for its art-recognized meaning to indicate that the protein is produced at higher than trace levels that can be detected by sophisticated analytical techniques but that cannot otherwise [be] separated from the milieu in which they are produced."

In the Toman declaration, submitted by Velander, the declarant defines a "useful" amount of transgenically produced fibrinogen as "actually any amount because it would be free of human pathogens" (¶7). Hence, "recoverable amounts" in context means more than minuscule trace amounts.

g. Claim 65 is not limited to the use of any specific "additional DNA segments required for [fibrinogen] expression in the mammary gland of a host female mammal." In particular, it is not limited to the use of any particular promoter.

h. Claim 65 is not limited to a mammal that can reliably pass all of the DNA segments as a group to its progeny.

i. Claim 65 is not limited to livestock animals.

j. According to Garner, the critical date for assessing patentability under § 102(b)/§ 103 is 18 February 1993, one year before the filing date of Velander's 068 application (Paper No. 22 at 6, ¶7, and at 17 n.*).

k. As of that critical date, human fibrinogen had been characterized as a hexameric protein comprising two copies each of Aα, Bβ, and γ polypeptide chains, which were expressed, assembled, and secreted together by liver cells. Part of the expression and assembly processes includes post-translational modifications (Paper No. 22 at 6, ¶9 (uncontested)).

l. As of the critical date, the cDNA and genomic DNA sequences for all three chains had been published (Paper No. 22 at 7, ¶11 (uncontested)).

m. As of the critical date, biocompetent[3] human fibrinogen had been produced using cultured[4] mammalian cells transfected with the cDNAs encoding the three chains (Paper No. 22 at 7, ¶12 (uncontested)).

n. As of the critical date, several introduced proteins had been produced in the milk of transgenic mammals. The prior art included teachings or suggestions for the production of blood and serum proteins in the milk of transgenic mammals (Paper No. 22 at 10-11, ¶16).

o. As of the critical date, genomic DNA was generally preferred over cDNA because it produces higher expression levels in transgenic animals (Paper No. 22 at 14, ¶23 (uncontested)).

p. Garner has demonstrated the existence of all of the elements of claim 65 in the prior art, albeit not in a single reference, and has demonstrated a motivation to produce serum proteins, including fibrinogen, in the milk of a transgenic animal.

q. Velander disputes the level of skill in the art and urges (Paper No. 41 at 3-4, footnote omitted) that

> the ordinary skilled worker would have had more than just mere 'familiarity' with transgenics. Rather, the skilled person would have had experience in expressing heterologous proteins in transgenic animals and in obtaining the expressed heterologous proteins from the body fluids of the animals, particularly from milk. The skilled worker actually should have had experience as a member of a laboratory group that produced, identified and used transgenic animals to express heterologous proteins in the body fluids of transgenic animals, particularly in the mammary glands of transgenic animals.

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[3] Biologically active for its intended purpose.

[4] Grown in vitro.

For the purposes of this decision, we will adopt Velander's view that a person having ordinary skill in the art as of the critical date would have been knowledgeable and experienced in the expression of heterologous proteins in the milk of transgenic animals.[5]

r. Velander contends that there is no nexus between the type of DNA used and the level of expression. Since claim 65 is generic to both cDNA and genomic DNA, this issue will be treated later with regard to Garner's reissue claims.

s. Velander's main point of opposition is that a person having ordinary skill in the art would not have had a reasonable expectation of success based on the teachings in the art as of the critical date.

When the prior art seems to point in the direction of the claimed invention, care is required to ensure that the claim is not improperly held unpatentable for what was only "obvious to try", e.g., exploring a new technology or general approach that seemed promising, when the prior art gives only general guidance. However, obviousness under § 103 only requires a reasonable expectation of success. In re O'Farrell, 853 F.2d 894, 904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (finding a reasonable expectation of success). Whether there was a reasonable expectation of success is assessed from the perspective of the person of ordinary skill in the art. The inventors' ultimate success is irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success. Life Tech., Inc. v. Clontech

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[5] The record also contains testimony regarding the degrees and work experience of the hypothetical person having ordinary skill in the art, but that sort of evidence is not nearly as probative as the testimony regarding what the person having ordinary skill in the art would have actually known or been able to do. Accord Argyropoulos v. Swarup, 56 USPQ2d 1795, 1807 (BPAI (ITS) 2000) (non-precedential). Note that Velander may be urging a high level of skill in the art in response to Garner's motion to change inventorship. Nevertheless, the level of skill in the art cannot be high for the purpose of determining inventorship, but something else for the purpose of obviousness.

Labs., Inc., 224 F.3d 1320, 1326, 56 USPQ2d 1186, 1191 (Fed. Cir. 2000) (finding no reasonable expectation of success).

t. Garner's initial witness, Alan Colman, was a colleague of Garner inventors Ian Garner and Michael Dalrymple.

Testimony of a co-worker regarding what was generally known in the art must be considered with caution. Cf. Refac Int'l, Ltd. v. Lotus Dev. Corp., 81 F.3d 1576, 1581, 38 USPQ2d 1665, 1669 (Fed. Cir. 1996) (finding unreported relationship between affiant and patentees to have been highly material). A colleague who has worked or consulted on a course of research may have significant insights into that resulting invention beyond the knowledge of one ordinarily skilled.

u. Colman testified that "the skilled worker, on [the critical] date, would reasonably have expected transgenic animals produced using cDNAs encoding the Aα, Bβ , and γ chains, respectively, of fibrinogen to produce biocompetent fibrinogen at about the same level per cell as had been produced in mammalian cell cultures using those cDNAs." (1st Colman Dec. at ¶10.)

v. Colman testified that "the skilled worker, on [the critical] date, would reasonably have expected transgenic animals produced using genomic DNAs encoding those fibrinogen chains to produce no more than that [cell culture] level per cell." (1st Colman Dec. at ¶10.)

Broad conclusory statements offered by experts are not evidence and are not sufficient to establish a genuine issue of material fact. Telemac Cellular Corp. v. Topp Telecom, Inc.,

247 F.3d 1316, 1329, 58 USPQ2d 1545, 1554 (Fed. Cir. 2001); Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 294, 227 USPQ 657, 665 (Fed. Cir. 1985) ("Lack of factual support for expert opinion going to factual determinations, however, may render the testimony of little probative value in a validity determination."); Carella v. Starlight Archery and Pro Line Co., 804 F.2d 135, 138, 231 USPQ 644, 646 (Fed. Cir. 1986) (Unsupported testimony "must be regarded with suspicion and subjected to close scrutiny."). Colman's testimony is accorded little weight except where it is supported by cited literature.

w. Colman cites a prior-art Hennighausen review[6] (GX29[7]) as indicative of a reasonable expectation of success.

x. The Hennighausen review provides a general overview of the use of transgenic mammals to produce foreign proteins in milk. The review touts the advantages of transgenic milk production over cell cultures (p. 3). It identifies serum proteins, especially blood clotting factors, as ideal proteins for development (p. 4).

y. According to the Hennighausen review, success had already been achieved for several human proteins, including serum proteins like protein C, but at widely variable and generally low expression levels (pp. 5-6). The review notes that production was then possible, but not economically effective (p. 7). It notes the high costs, long delays, low yields of transgenic animals, difficulties with proper gene regulation, and protein purification (p. 7) as

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[6] Lothar Hennighausen, "The Mammary Gland as a Bioreactor: Production of Foreign Proteins in Milk", 1 Protein Expr. & Purif. 3-8 (1990).

[7] "GX" indicates a numbered Garner exhibit; "VX", a number Velander exhibit.

continuing problems. The review notes that better results are often obtained by using genomic DNA since the introns can contain valuable regulatory information (pp. 4, 5, and 6).

z. The review creates the impression that producing transgenic mammalian livestock is expensive, technically challenging, and laborious, but nevertheless a viable option for producing proteins. It also touts the use of mice as a test system (p. 7).

aa. Velander claim 65 is not limited to livestock, but is broad enough to include mammals like mice.

bb. Colman also cites a prior-art Meade patent[8] (GX30) as showing a reasonable expectation of success.

cc. Meade teaches the production of foreign (exogenous) proteins in the milk of transgenic mammals (1:53-2:12).

dd. Meade provides motivation to switch from cell cultures to transgenic milk production, noting cost advantages (1:15-21) and increased reliability (1:41-45), and (vis-a-vis prokaryotes) proper post-translational modifications (1:36-41).

ee. Meade identifies many proteins subject to its method, including serum proteins (3:31-40).

ff. Velander provided declarations from Hennighausen, Rosen, and Toman regarding the expectation of success.

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[8] H. Meade & N. Lonberg, "Isolation of exogenous recombinant proteins from the milk of transgenic mammals", 4,873,316 (issued 1989).

gg. Hennighausen is the author of Garner exhibit 29 (GX29) and Velander exhibit 16 (VX16), an analysis article.[9] The Hennighausen article (VX16) is not prior art.

hh. As with Colman, Hennighausen's broad conclusions are entitled to little weight beyond the corroborating references he cites. Moreover, Hennighausen's litigation-driven testimony is accorded less credence than his ante litem motam writings.

The Hennighausen article (VX16), however, is of limited probative value since it was written well after the critical date. Obviousness, and expectation of success, are evaluated from the perspective of a person having ordinary skill in the art at the time of the invention. While later publications may explain what was known earlier, it would be wrong to impute later-recognized insights—or possible obstacles—to the knowledge available to those skilled in the art at the time of the invention. Cf. In re Koller, 613 F.2d 819, 824 n.5 & text, 204 USPQ 702, 706 n.5 & text (CCPA 1980) (discussing the "narrow circumstances" in which later publications could permissibly be used to show earlier knowledge). One skilled in the art could not be daunted by unknown obstacles although the subsequent publications might be relevant to show that the obstacles actually applied to the specific problem facing the inventor. The Hennighausen article is not that specific.

ii. The Hennighausen article teaches that as of 1997 production of proteins using transgenic animal milk was possible, even for complex proteins, large-scale production was still elusive. It identified two obstacles to *large-scale* use: variable production and problems in post-translational modifications for some proteins. The first problem was solvable

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[9] L. Hennighausen, "Transgenic factor VIII: The milky way and beyond", 15 Nature Biot. 945-47 (1997).

in mice, but not yet established in livestock. The second problem was only stated to be an issue when high levels of protein were produced since it could overwhelm the tissue's "enzymatic machinery" for introducing sophisticated post-translational modifications (VX16 at 946).

In this regard, it is important to recall that claim 65 is not limited to livestock mammals or to a particularly high level of production.[10] Moreover, variability in results does not mean there was no reasonable expectation of success. E.g., In re Longi, 759 F.2d 887, 897, 225 USPQ 645, 651-52 (Fed. Cir. 1985).

jj. Hennighausen's testimony suggests that protein recovery could be difficult for some proteins (¶ 6), but does not explain why one would have expected fibrinogen to be one of those problematic proteins. The Hennighausen review (GX29 at 7) suggests that the problem would be readily solvable. Other publications (e.g., VX18[11] at 281) also indicate that the concern is overstated.

kk. Hennighausen's testimony also indicates that the transgenes can cause deleterious effects on the transgenic animal or its offspring. The testimony does not point a

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[10] Note that if claim 65 were construed to require reliable, commercially economical levels of production, then Velander's evidence would raise serious questions about whether Velander's disclosure enables such levels of production. See, e.g., Hennighausen Dec. ¶ 6.

[11] L.-M. Houdebine, "Minireview: Production of pharmaceutical proteins from transgenic animals", 34 J. Biot. 269-287 (1994). Note that Houdebine reports (at 274) that the use of introns in transgenic animals is "essential in most cases".

specific portion of the articles cited (VX6,[12] VX37[13], VX28[14]). In any case, the articles do not teach that the technology is unworkable, but rather that expression of a specific protein, whey acidic protein (WAP), which is a common milk protein, can cause specific problems leading to impairment or loss of lactation. Velander and the Hennighausen testimony fail to provide any basis for generalizing this problem to other proteins. Moreover, the articles show that some successful transgenic animals are produced, which means that success can be reasonably expected, but at a higher cost (since more animals will have to be produced and screened to ensure success).

ll. Hennighausen's testimony notes that cell culture results do not necessarily correlate to transgenic animal results (¶12). No precise correlation is required for a reasonable expectation of success. Moreover, the articles (VX11[15], VX38[16]) cited for corroboration are inapposite. Neither purports to show that cell culture success will not translate recoverable amounts of protein expression in transgenic animals. Rather, the articles report that expression *enhancers* do not necessarily operate the same way in cell cultures and transgenic animals. In the

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[12] T. Burdon et al., "Over-expression of an endogenous milk protein gene in transgenic mice is associated with impaired mammary alveolar development and a *milchlos* phenotype", 36 Mechs. Dev. 67-74 (1991) (Hennighausen is the corresponding author).

[13] R.J. Wall et al., "High-level synthesis of a heterologous milk protein in the mammary glands of transgenic swine", 88 Proc. Nat'l Acad. Sci. (USA) 1696-1700 (1991) (Hennighausen is the corresponding author).

[14] A. Shamay et al., "Expression of the whey acidic protein in transgenic pigs impairs mammary development", 1 Transgenic Res. 124-132 (1992) (Hennighausen is the corresponding author).

[15] P.A. Furth et al., "The variability in activity of the universally expressed human cytomegalovirus immediate early gene 1 enhancer/promoter in transgenic mice", 19 Nucleic Acids Res. 6205-08 (1991) (L. Hennighausen is a co-author).

[16] C.B.A. Whitelaw et al., "Targeting expression to the mammary gland: intronic sequences can enhance the efficiency of gene expression in transgenic mice, 1 Transgenic Res. 3-13 (1991).

Whitelaw article (VX38), the use of introns is described as improving transcription yields in transgenic mice,[17] but not in a baby hampster kidney fibroblast cell culture. The Furth article (VX11) was not directed to transgenic milk production. It indicated that the viral transcription enhancer used worked in transgenic animals although the level of production varied from tissue to tissue and from animal to animal. Hennighausen's testimony also notes (¶13) that expression of human tissue plasminogen activator is much higher in transgenic animals than in cell cultures (see VX12[18]).

mm. The dispute about the extent to which cell culture results can be extrapolated to transgenic animals is largely irrelevant. At the critical date, a person having ordinary skill in the art would have had ample motivation to switch to a transgenic system, including an expectation of superior yields, without need for a precise prediction of the yields in the transgenic system.

nn. Hennighausen's testimony indicates that purification may be a problem (¶16), but the cited 1987 Gordon article actually purports to show that expressed protein is "sufficiently stable in milk" (VX12 at 1185). Hennighausen testimony does not point to a specific problem in Gordon or explain why Gordon's reported experience in 1987 would have daunted a person having ordinary skill in the art at the critical date.

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[17] An important finding regarding the advantages of using genomic DNA in trangenic animals.

[18] K. Gordon et al., "Production of human tissue plasminogen activator in transgenic mouse milk", 5 Biotech. 1183-87 (1987) (Hennighausen is a co-author).

oo. The Hennighausen testimony postulates potential difficulties and unsatisfactory production levels, but the broad conclusions of Hennighausen's testimony are not credible when compared to the references cited for corroboration.

pp. Rosen is a co-author of Garner exhibit 7 (GX7[19]) and the inventor of Garner exhibit 37 (GX37[20]).

qq. As with the other declarants, Rosen's broad conclusions are entitled to little weight beyond the corroborating references he cites. Moreover, Rosen's litigation-driven testimony is accorded less credence than his ante litem motam writings.

rr. Rosen's declaration is credible where he declares (¶18), "in 1993, it would [have been] obvious to combine [the DNA sequences encoding the three fibrinogen chains and regulatory sequences requisite for expression in the mammary gland] to target expression to the mammary gland. The only issue would have been which promoter or regulatory sequences to use from the known promoters and regulatory sequences." This testimony is consistent with the other publications of record.

ss. Rosen's declaration (¶¶7 & 8) that fibrinogen was "more complex than any transgenic expression previously attempted" is credible to the extent that it is understood to mean fibrinogen involves the assembly of more protein subunits than the other proteins. Rosen points to Meade (GX30), Clark (GX31[21]), and Rosen (GX37) for support, but does not identify how

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[19] N.M. Greenberg et al., "Expression of biologically active heterodimeric bovine follicle-stimulating hormone in milk of transgenic mice", 88 Proc. Nat'l Acad. Sci. (USA) 8327-31 (1991).

[20] Rosen, "DNA sequences to target proteins to the mammary gland for efficient secretion", U.S. Patent 5,304,489 (1994) (eff. filing date 1987).

[21] A.J. Clark, "Peptide production", WO 88/00239 (1988).

those references provide support for his contention. Assuming, Rosen means that the proteins in those references involve fewer protein subunits, the declaration does not explain why one skilled in the art as of the critical date would therefore have expected not to succeed. Moreover, Rosen's testimony is hedged with qualifications (emphasis added) like "should not be *completely* equated" (¶7) and "should not be considered *predictive*" (¶8).

Obviousness does not require absolute predictability of success. O'Farrell, 853 F.2d at 904, 7 USPQ2d at 1681.

tt. Rosen's declaration focuses on the variability of expression levels (¶¶9-12 & 14-16), but does not connect that variability with the limitations of Velander's claims.

Variability in results does not mean there was no reasonable expectation of success. Longi, 759 F.2d at 897, 225 USPQ at 651-52.

uu. The Rosen declaration notes (¶13) that cell lines cannot predict adverse effects of expression on transgenic animals, citing Yarus (VX40).[22] Yarus was published after Garner's effective filing date and the critical date. The declaration does not point to any specific part of Yarus that suggests, and does not itself suggest, that one skill in the art would have considered any of these problems as insurmountable. Like the Rosen declaration, Yarus hedges on the unpredictability: "mammary development and lactation are complex processes whose regulation is not *totally* understood" (at 59, emphasis added).

vv. Rosen's declaration read as a whole suggests that all of the components for making the invention were in place as of Garner's filing date, but that it would have been unlikely

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[22] S. Yarus, "Engineering transgenes for use in the mammary gland", 18 Genet. Eng'g 57 (1996) (Rosen is a co-author).

that one *lacking* the high level of skill in the art could have successfully implemented the invention.

ww. The Toman declaration repeats the themes that expression in transgenic animals is variable and that cell lines are not "predictive" of expression and problems in transgenic animals (¶8-12). The declaration does not connect these themes to the actual limitations of the claims.

xx. Toman notes the relative complexity of fibrinogen, but concerns raised (¶13) relate to optimization of expression, not the expectation of success. Moreover, Toman does not point to any basis for supposing that any of the concerns were likely. For instance, Toman notes as a problem "the assembly of a multimeric protein in a cell which normally doesn't process this molecule, e.g., 29 sulfhydryl bonds have to be formed correctly", but does not provide any objective basis for expecting failure on this basis. Toman does not even provide a basis for supposing that such assembly must occur in the cell before secretion of the components. Other problems, such as the clogging of ducts with polymerized proteins or unintended expression of the protein are plainly not unique problems confronting fibrinogen expression. Toman's declaration is starkly at odds in tone with the contemporaneous literature.

yy. Toman's conclusion that the art was unpredictable and offered little chance of success is must be read in light of Toman's focus on predictable expression levels and the lack of correlation with cell lines, neither of which are limitations of claim 65. Moreover, Toman's conclusion is less credible than the wealth of contemporaneous publications offering a contrary view.

zz. It is worth noting that Velander witnesses consistently point to the variability of expression to indicate that the art was not predictable, but also rely on that variability to discount Garner's contention that genomic DNA yields unexpectedly good results. The cited publications collectively indicate that, at the critical date, a person having ordinary skill in the art would have expected considerable variability in yields (including no yield), even among animals subjected to the same protocol. A person having ordinary skill in the art would have viewed such variability as an indication of the expense, time, and effort involved in producing transgenic mammals and selecting those with "recoverable" yields, but not as an indication that success would be unlikely.

aaa. Garner's declarant Colman acknowledges the complexity of fibrinogen, but states that that complexity was understood as of the critical date (1st Colman Dec. at ¶13) and concludes (¶20) that a person having ordinary skill in the art would have expected success without undue experimentation based on what was known and suggested in the art (¶¶14-19).

bbb. Velander points to Garner's response to an office action (VX29 at 10) in which Garner uses the complexity of fibrinogen to overcome the rejection. The rejection and response, however, focused on the teaching of expression of fibrinogen in cell cultures. Garner argued that cell cultures were not predictive of expression levels in transgenic animals. The evidentiary value of this attorney argument is questionable at best, but more to the point it simply states the already accepted fact that cell cultures do not predict expression levels in transgenic animals. Whether or why the examiner might have found this argument relevant or persuasive is a point we need not decide here.

Garner bears the burden of justifying the relief it seeks. For this motion, the preponderance of the evidence supports the findings that the level of skill in the art was high; all of the elements of the invention, including the DNA, the promoters, and the experience with transgenic animals existed in the prior art; and the art provided ample motivation for one skilled in the art to attempt to produce transgenic animals engineered to express human fibrinogen. One skilled in the art would have expected the process to be challenging, expensive, time-consuming, and tedious, but would not have expected the process to require undue experimentation. Furthermore, one skilled in the art would have been well acquainted with the inadequacy of cell cultures as a basis for predicting success in transgenic animals and thus would not have counted on such results to provide much encouragement or discouragement. Finally, absolute predictability is not a requirement for obviousness. Hence, the findings above support the conclusion that Velander claim 65, and by extension all of Velander's involved claims and Garner's involved claims were unpatentable under § 103 as of the critical date.

Since Garner's preliminary motion 2 is granted, the motions contingent on its denial (Garner preliminary motions 4, 5, and 7, its miscellaneous motion to accept belated preliminary motion 7, and Velander's preliminary motions 3-7) are dismissed as moot.

2. Preliminary motion 3 (Paper No. 23)

a. Garner moves to substitute proposed G-1 contingent on the granting of Garner preliminary motion 2.

b. Proposed count G-1 is substantially identical to count 1 except for two key differences:

i. the DNA is limited to *genomic* DNA and

ii. there is a fourth alternative—

A set of DNA sequences comprising:

a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain, the DNA segment comprising genomic DNA encoding the Aα chain;

a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bβ chain, the DNA segment comprising genomic DNA encoding the Bβ chain; and

a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen γ chain, the DNA segment comprising genomic DNA encoding the γ chain, wherein each chain is from the same species, and wherein each of said first, second and third segments is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal.

c. Garner argues that the genomic embodiment of the interfering subject matter is patentable over the prior art because it provides unexpectedly high yields.

d. Garner argues that the count should include the fourth "constructs" alternative because it would permit Garner to rely on its best proofs of priority.

e. Garner acknowledges that the prior art prefers the use of genomic DNA in transgenic animals, but argues that the art also indicates problems with *over*expression in transgenic animals using genomic DNA (Paper No. 23 at 10-12).

f. As discussed in the context of Garner preliminary motion 2, there is ample evidence that the prior art taught the use of genomic DNA in transgenic animals would be expected to provide higher expression. Garner concedes as much (Paper No. 69 (G. Rep. 3) at 3).

g. Velander argues that there is no nexus between the type of DNA used and the amount expressed and recovered since other factors, like the number of DNA segments incorporated into the animal's chromosome (copy number) also affect expression levels (Paper No. 42 (V. Opp. 3) at 4-5).

h. Velander also notes that expression levels in this art are extremely variable (Paper No. 42 at 5-6).

i. The variability of expression was well-documented in the literature as discussed for Garner preliminary motion 2.

j. Velander also argues that the constructs alternative is a separate invention and an unpatentable one at that (Paper No. 42 at 7-8).

As movant, Garner bears the burden of justifying the substitution of the count. Moreover, in arguing for patentability based on unexpected results, a secondary consideration, Garner bears the burden of proof for those unexpected results. The results must be unexpected compared to the closest prior art. Recognition of an latent property is not a basis for rebutting a prima facie finding of obviousness. In re Baxter Travenol Labs., 952 F.2d 388, 392, 21 USPQ2d 1281, 1285 (Fed. Cir. 1991).

k. The first question is what is the closest prior art? There are three choices: cell cultures with genomic DNA, transgenic animals with cDNA, or transgenic animals with genomic DNA. As discussed previously, the art teaches that cell cultures are very different systems from transgenic animals and that cell cultures do not reliably predict outcomes in transgenic animals. Consequently, the closest prior art must be some kind of transgenic animal.

l. Garner argues that the closest prior art is Velander's examples using cDNA in transgenic animals (Paper No. 23 at 14). There are three problems with this comparison:

i. First, the art points to genomic DNA as preferred in transgenic animals because it produces higher yields. Hence, the "closest" implementation taught or suggested in the prior art is the use of genomic DNA in transgenic animals. Choosing cDNA as the closest prior art skews the comparison by choosing the alternative—cDNA—that the art teaches is likely to underperform in precisely the comparison being made—yields in transgenic animals. In short, Garner's "unexpected result" is an inherent property of the preferred prior art approach.

Recognition of an latent property is not a basis for rebutting a prima facie case for obviousness. Baxter Travenol, 952 F.2d at 392, 21 USPQ2d at 1285. Indeed, just as unexpected beneficial results suggest unobviousness, expected beneficial results suggest obviousness. In re Skoll, 523 F.2d 1392, 1397, 187 USPQ 481, 484 (CCPA 1975).

ii. Garner provides attorney argument that Velander's cDNA results are the closest prior art, but does not offer any comparison between the methodology of Velander and Garner. Garner does not appear to have made out a prima facie showing that the actual methods are sufficiently the same to allow for any meaningful comparison. Essentially, Garner assumes the methods are comparable without any showing or testimony to support this supposition. Consequently, it is not possible to determine whether differences in methodologies could explain the differences in yields without having the panel perform the comparison on its own.

Garner does point to large blocks of Velander's applications, but it is not the job of the board to identify the relevant portions of Velander's applications, Garner's patent and papers, and then determine whether they are comparable in the first instance. In re Swartz, 232 F.3d 862, 864, 56 USPQ2d 1703, 1704 (Fed. Cir. 2000). It is not the obligation of the panel to perform the role of advocate for one of the parties.

iii. Finally, the sample sizes—a few mice in each case, and only one with recovery in excess of 1 mg—are tiny. Given the extreme variability in expression suggested in the art, the comparison presented appears to be statistically meaningless.

m. Garner suggests that the prior art teaches away from the use of genomic DNA because *over*expression can overload the cellular protein expression, assembly, and secretion machinery (Paper No. 23 at 10-12). As an initial matter, this argument contradicts the teachings in the prior art as well as Garner's admission that genomic DNA was preferred. Known problems that do not overcome the preference in the art for genomic DNA hardly qualify as a teaching away. Moreover, Garner's evidence is equivocal.

i. The Prunkard abstract (GX35)[23] notes that there are differences between a human liver cell line and a hamster kidney cell line. Given the understood differences between cell lines and transgenic animals, it is unclear what—if anything—one skilled in the art would have concluded from Prunkard regarding expression in transgenic animal mammaries.[24]

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[23] D. Prunkard & D. Foster, "High level secretion of recombinant human fibrinogen in BHK cells is limited by a post-transcriptional process", J. Cell. Biochem. 15 (supp. 17C, 1993) (abstract H 123).

[24] Elsewhere (Paper No. 67 (G. Rep. 1) at 15), Garner relies on the Prunkard article to show that variable rates of expression of the different fibrinogen chains was not a cause for concern since some biocompetent fibrinogen was still produced.

ii. The Hurtley article (GX34)[25] is thirty pages long and Garner has not pointed to a specific part it wishes to have considered. On its face the article points out many issues in the production of secreted proteins. Garner has not pointed to any specific issue of relevance to the use of genomic DNA in transgenic animals. The article appears to be a survey of the knowledge in the secreted protein art in 1989, and does not appear to speak directly to the choice between genomic DNA and cDNA. The general understanding in the art is presumably reflected in the assessments made by subsequent authors that genomic DNA would be preferred for the production of proteins in transgenic animal milk. Again, their preference for genomic DNA despite known problems with protein expression systems is evidence of obviousness, not of teaching away.

iii. The Drohan article (GX38)[26] appears to be directed to the use of human protein C (HPC) cDNA in mice (at 356). Drohan reported evidence of improper glycosylation, which resulted in less active (as opposed to inactive) HPC. The article clearly shows that biocompetent (i.e., active) HPC was produced in recoverable amounts.

iv. Again, it is important to focus on the language of the count. The resulting fibrinogen must be biocompetent and produced in recoverable amounts. One skilled in the art as of the critical date would have expected to be able to produce biocompetent fibrinogen in recoverable amounts, even though some problems would likely be encountered and the results might not be optimal.

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[25] S.M. Hurtley & A. Helenius, "Protein oligomerization in the endoplasmic reticulum", 5 Annu. Rev. Cell Biol. 277-307 (1989).

[26] W.N. Drohan et al., "Inefficient processing of human protein C in the mouse mammary gland", 3 Transgenic Res. 355-364 (1994) (three of the Velander inventors are co-authors).

n. Since the genomic DNA alternatives of the count would have been obvious in view of the prior art, Garner's proposed count G-1 is defective regardless of the merits of the fourth constructs alternative of the count. For the sake of completeness, however, it should be noted that the genomic DNA constructs are necessary precursors for the method and mammal alternatives of the count. All of the methods in the prior art for creating transgenic animals use such constructs for the proteins of interest. Note too that the broadest reasonable construction of the fourth alternative of the count does not distinguish between three separate segments in different vectors, three separate segments on the same vector, or other similar variations.

On balance, Garner has not carried its burden for justifying the substitution of a new count. All of the variants of the count would have been obvious to one skilled in the art as of the critical date. Since Garner's preliminary motion 3 is denied, Velander's contingent preliminary motions 2 and 5 are dismissed as moot.

3. Preliminary motion 1 (Paper No. 21)

a. Garner moves to add its 09/232,488 ("488") application to the interference. The 488 application is a reissue application of Garner's 940 patent. All of the independent claims are have been amended as shown in Addendum A of this decision (with additions underlined) to further limit the claims to genomic DNA.

b. The reissue claims are identical to the involved Garner claims with two exceptions:

i. They are limited to genomic DNA, and

ii. Claim 34 is new and is the same as the constructs alternative of Garner's proposed count G-1. Consequently, the issues relating to this motion closely follow the issues in Garner preliminary motion 1.

c. According to Garner—

i. Its 940 patent claims encompass the use of cDNA, which Garner contends would have been obvious to a person having ordinary skill in the art, and thus the 940 patent claims are not patentable (GX15, ¶¶6-9). According to Garner, the further limitation of the claims to the use of genomic DNA corrects the problem because genomic DNA produces unexpectedly good results.

ii. Its 940 claims failed to claim a set of DNA sequences necessary to thwart domestic production of sequences for use in foreign production of fibrinogen. To avoid this threat to its scope of protection, Garner has added claim 34 (see Addendum A).

d. Garner stipulates that all of the reissue claims correspond to the count, despite the fact that they are at least partially narrower, and the fact that Garner contends the narrowing amendments make the claims patentable while the count is not patentable subject matter.

e. Garner does not provide separate arguments for the patentability of its reissue claims, so they will be treated as standing or falling together (see, e.g., Paper No. 21 at 11).

f. Velander opposes the motion (Paper No. 40) because—

i. According to Velander, the reissue application corrects no error because the use of cDNA would not have been obvious at the time of Garner's invention, there is no nexus between the type of DNA used and the resulting level of protein expression, and genomic DNA results are not unexpectedly good;

ii. According to Velander, the subject matter of new claim 34 would have been obvious to a person having ordinary skill in the art at the time of Garner's invention;

iii. According to Velander, Garner's concern about domestic preparation of sequences for use in foreign production is misplaced because reimportation is addressed by 35 U.S.C. § 271(g) and protection in foreign countries must be addressed through foreign patent protection;

iv. According to Velander, creating transgenic animals requires considerable skill and results from cell cultures are not predictive of transgenic animal results;

g. Garner's stipulation that the reissue claims all correspond to the count is accepted, albeit not entirely for the reasons Garner provides. Rather, as discussed in previous sections, as of the critical date the genomic DNA subject matter would have been obvious to one skilled in the art.

In view of our decisions on Garner's preliminary motions 2 and 3, its motion to add its reissue application and claims appears to be moot since their subject matter is unpatentable. One option would be to deny the motion and leave it to the examiner, pursuant to 37 C.F.R. § 1.659(c). In the present case, however, the issue has been fully and fairly raised and briefed. Consequently, in the interests of completeness and administrative efficiency, the board exercises

its discretion to add Garner's reissue claims and hold them unpatentable as part of this interference. The fact that the claims are unpatentable for the reasons given in this opinion, or for the separate reasons Velander has suggested, is not a procedural bar. Although a patentable claim is necessary to declare an interference in the first instance, once declared, all claims defining the same subject matter correspond to the count regardless of their patentability. 37 C.F.R. § 1.606. Garner's preliminary motion 1 is granted, but the claims of the reissue application are unpatentable.

4. Preliminary motion 6 (Paper No. 26)

a. Garner moves to have Velander claims 74-95 designated as corresponding to the count.

b. Velander has not opposed Garner preliminary motion 6.

c. Neither party has addressed the patentability of Velander claims 74-95.

d. One could infer from the Garner's arguments for designating the claims as corresponding, which are based on Velander's arguments to the examiner, that Velander has conceded that the claims are not separately patentable from Garner's 940 patent claims.

e. One could also infer from Garner's argument that the claims are silent regarding the secretion signal, that they are broader than Velander's claims that have already been held unpatentable.

f. Velander claims appear to have more differences than these from either the Garner 940 patent claims or Velander claims 64-73.

g. The examiner had indicated that the claims do correspond to the count (Form PTO-850).

h. The examiner also indicated that the claims do not correspond to the count because they are unpatentable because the lack enabling support (Rule 609(b) stmt. ¶7a).

As noted above, patentability is not necessary for correspondence. Nevertheless, the examiner has already indicated Velander claims 74-95 to be unpatentable, so they would not provide any independent basis for continuing the interference. Moreover, their patentability (or not) with respect to the prior art has not been developed by either party. Absent a specific concession from Velander,[27] the panel is reluctant to rule on the patentability of these claims without any development specific to these claims in the record. Consequently, Garner preliminary motion 6 is dismissed as moot.

D. VELANDER'S PRELIMINARY MOTION 1 (PAPER NO. 32)

1. Velander moves to add claims 96-101 to its 184 application and to have those claims designated as corresponding to the count.

2. Claims 96-98 are limited to genomic DNA; claims 99-101, to cDNA.

3. Velander argues that the claims are necessarily directed to the same invention as the count, which simply recites "DNA" (at 6).

As a formal matter, Velander's analysis is backwards. Since genomic DNA and cDNA are species of the DNA genus, it does not automatically follow that generic DNA would have

[27] Note that Velander's failure to oppose the correspondence of the claims to an unpatentable count is not the same as a concession that the claims themselves are not patentable. E.g., In re Van Geuns, 988 F.2d 1181, 1184, 26 USPQ2d 1057, 1059 (Fed. Cir. 1993) (patentability of claims must be analyzed separately from patentability of count).

rendered genomic DNA or cDNA obvious. In this context, however, it appears that those skilled in the art would have understood genomic DNA and cDNA to be essentially the only two species in the DNA genus. In any case, Velander's stipulation that they are the same patentable invention is accepted.

4. Garner opposes the addition of claims 96-98 (Paper No. 52), contingent (at 2-3) on the granting of Garner preliminary motion 2. According to Garner, both genomic DNA and cDNA claims are obvious over the prior art and Velander teaches away from the use of genomic DNA and lacks any support for unexpected results.

Absent any evidence to the contrary, an applicant must at least demonstrate substantially improved results and state that the results were unexpected. In re Geisler, 116 F.3d 1465, 1470-71, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

5. Velander presumably fails to show unexpected results because, while it believes its claim subject matter to be patentable, it has consistently rejected Garner's contention that Garner's results with genomic DNA are unexpected.

6. More troubling is Velander's failure to provide any reason for adding the claims that is related to the fair and efficient administration of this interference. Unlike Velander's parallel preliminary motion 3, which responds to proposed changes in the count, Velander provides no reason for this motion. If their scope is essentially the same as existing claims, since the count has not changed, there is no reason to grant this motion. If the scope is different, the panel should not be left to guess what that difference means.

7. Moreover, the claims have not been examined[28] and, in view of the preceding portions of this opinion, might not be patentable. If the claims have substantially the same scope as the currently involved claims, then they are most likely unpatentable.

As movant, Velander must justify the relief it seeks. Velander has not provided the reason for adding these claims. Since they do not appear to affect the scope of the count and since they may well be unpatentable, they will not be added. Velander's preliminary motion 1 is denied.

E. VELANDER'S MOTION TO STRIKE

1. Velander moves to strike (Paper No. 84) a definition of "recoverable amount" offered in the second Colman declaration (Paper No. 73 at 2 n.**), as well as portions of other papers that rely on that definition—

a. Declaration of Richard F. Lathe at 3 n.*,

b. Declaration of Bruce Sean Munro at 3 n.*,

c. Garner Reply 1 at 4 n.2, and

d. Garner Reply 2 at 4 n.2.

2. According to Velander, the definition was offered late (after oppositions were filed) and was not responsive to any point raised in opposition. Consequently, Velander states that it was prejudiced.

3. Garner insists (Paper No. 86) that it was in response to references in the claims and count, and attendant arguments in the oppositions, regarding what biologically active means.

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[28] Note that claims 96, 98, 99, and 101 are not limited to human fibrinogen.

4. Velander's motion is essentially granted for two reasons—

a. First, it came too late. A term that appears in claims of both parties and in the count should not be defined for the first time in the replies (and their exhibits) absent some compelling reason. While the definition arguably responds to arguments in opposition, the term in question is also central to Garner's contention that Velander's claims and the count are unpatentable.

b. A second, and independent, reason for granting relief is that the definition comes with absolutely no support. It is far more detailed than the definition explicitly provided in Garner's prosecution history (VX29 at 9), discussed earlier. Thus, it not only changes the terms of the debate late in the proceeding, but it does so at odds with the position Garner took during prosecution. Expert testimony at odds with the intrinsic evidence in the case is entitled to very little, if any, weight.

On balance, the prejudice to Velander of admitting the late definition would be significant and unjustified if it were accorded any weight. Since it cannot be accorded much weight, striking it poses little prejudice to Garner. Accordingly, Colman's definition of "recoverable amounts" and those portions of papers relying on that definition are accorded no weight.

F. GARNER'S MOTION TO CORRECT INVENTORSHIP

1. Garner moved to correct its inventorship (Paper No. 20) by removing Garner and Dalrymple as inventors.

2. At the request of the parties, the issue was deferred until the priority phase since it was inextricably linked to priority (Paper No. 101).

3. At present, Garner does not have any patentable claims in its 940 patent or its reissue application.

Inventorship is determined with reference to the claimed invention. E.g., Pannu v. Iolab Corp., 155 F.3d 1344, 1351, 47 USPQ2d 1657, 1663 (Fed. Cir. 1998). Since Garner has no patentable claims, the question of inventorship is presently moot. Accordingly, Garner's motion to correct inventorship is dismissed as moot.

G. FURTHER PROCEEDINGS

Since neither side has any patentable claims involved, the next step would ordinarily be an order to show cause under 37 C.F.R. § 1.640(e). Both parties have had an opportunity to put on evidence and cross-examine opposing witnesses, so no additional testimony would be authorized. Consequently, any party seeking further administrative review should file a request for reconsideration in lieu of a response to an order to show cause.

ORDER

Upon consideration of the motions, it is—

ORDERED that Garner preliminary motions 1 and 2 be GRANTED;

FURTHER ORDERED that Garner reissue claims 1-34 be held UNPATENTABLE;

FURTHER ORDERED that Velander motion to strike be GRANTED to the extent that the Colman definition of "recoverable amount" be ACCORDED NO WEIGHT;

FURTHER ORDERED that Garner preliminary motion 3 and Velander preliminary motion 1 be DENIED;

FURTHER ORDERED that Garner motion to correct inventorship, Garner miscellaneous motion to file a belated motion, Garner preliminary motions 4-6, and Velander preliminary motions 2-7 be DISMISSED;

FURTHER ORDERED that judgment be entered against both parties as to count 1 and all involved claims unless a request for reconsideration is filed within **thirty (30) days** after the date of this decision;

FURTHER ORDERED that this interference be remanded to the administrative patent judge designated to handle the interference; and

FURTHER ORDERED that a copy of this decision be given a paper number and be entered in the administrative record of Garner's 5,639,940 patent and Velander's 08/443,184 application; and it is—

RECOMMENDED that the examiner of the Velander 08/443,184 application consider the patentability of claims 74-101 in view of this opinion.

M.K

FRED E. McKELVEY
Senior Administrative Patent Judge

RICHARD E. SCHAFER
Administrative Patent Judge

RICHARD TORCZON
Administrative Patent Judge

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Amended claims

1. A method for producing biocompetent fibrinogen comprising:
providing a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain, the DNA segment comprising genomic DNA encoding the Aα chain; a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bβ chain, the DNA segment comprising genomic DNA encoding the Bβ chain; and a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen γ chain, the DNA segment comprising genomic DNA encoding the γ chain, wherein each chain is from the same species, and wherein each of said first, second and third segments is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal;
introducing said DNA segments into a fertilized egg of a non-human mammalian species heterologous to the species of origin of said fibrinogen chains;
inserting said egg into an oviduct or uterus of a female of said mammalian species to obtain offspring carrying said DNA segments;
breeding said offspring to produce female progeny that express said first, second and third DNA segments and produce milk containing biocompetent fibrinogen encoded by said segments;
collecting milk from said female progeny; and
and recovering the biocompetent fibrinogen from the milk.

12. A method of producing biocompetent fibrinogen comprising:
incorporating a first DNA segment encoding a secretion signal operably linked to an Aα chain of fibrinogen into a β-lactoglobulin gene to produce a first gene fusion comprising a β-lactoglobulin promoter operably linked to the first DNA segment, the DNA segment comprising genomic DNA encoding the Aα chain;
incorporating a second DNA segment encoding a secretion signal operably linked to a Bβ chain of fibrinogen into a β-lactoglobulin gene to produce a second gene fusion comprising a β-lactoglobulin promoter operably linked to the second DNA segment, the DNA segment comprising genomic DNA encoding the Bβ chain;
incorporating a third DNA segment encoding a secretion signal operably linked to a γ chain of fibrinogen into a β-lactoglobulin gene to produce a third gene fusion comprising a β-lactoglobulin promoter operably linked to the third DNA segment, the DNA segment comprising genomic DNA encoding the γ chain, wherein each of said first, second and third segments are of the same species;
introducing said first, second and third gene fusions into the germ line of a non-human mammal so that said DNA segments are expressed in a mammary gland of said mammal or its female progeny and biocompetent fibrinogen is secreted into milk of said mammal or its female progeny;
obtaining milk from said mammal or its female progeny; and
recovering said fibrinogen from said milk.

18. A method for producing biocompetent fibrinogen comprising:
providing a transgenic female non-human mammal carrying in its germline heterologous genomic DNA segments encoding Aα, Bβ and γ chains of fibrinogen, wherein said segments are expressed in a mammary gland of said mammal and biocompetent fibrinogen encoded by said segments is secreted into milk of said mammal;
collecting milk from said mammal; and
recovering said biocompetent fibrinogen from said milk.

21. A transgenic non-human female mammal that produces recoverable amounts of biocompetent human fibrinogen in its milk, wherein said mammal comprises:
a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain, the DNA segment comprising heterologous genomic DNA encoding the Aα chain;
a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bβ chain, the DNA segment comprising heterologous genomic DNA encoding the Bβ chain; and
a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen γ chain, the DNA segment comprising heterologous genomic DNA encoding the γ chain; and
further wherein each chain is derived from the same species and is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal.

23. A process for producing a transgenic offspring of a mammal comprising:

providing a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain, the DNA segment comprising genomic DNA encoding the Aα chain; a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bβ chain, the DNA segment comprising genomic DNA encoding the Bβ chain; and a third DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen γ chain, the DNA segment comprising genomic DNA encoding the γ chain; wherein each chain is derived from the same species, and wherein each of said first, second and third segments is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal;

introducing said DNA segments into a fertilized egg of a non-human mammalian species heterologous to the species of origin of said fibrinogen chains;

inserting said fertilized egg into an oviduct or uterus of a female of said mammalian species; and

allowing said fertilized egg to develop thereby producing transgenic offspring carrying said first, second and third DNA segments, wherein female progeny of said mammal express said DNA segments in a mammary gland to produce biocompetent fibrinogen.

30. A non-human mammal carrying in its germline heterologous genomic DNA segments encoding human Aα, Bβ and γ chains of fibrinogen, wherein female progeny of said mammal express said DNA segments in a mammary gland to produce biocompetent human fibrinogen.

New claim

34. A set of DNA sequences comprising:

a first DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Aα chain, the DNA segment comprising genomic DNA encoding the Aα chain;

a second DNA segment encoding a secretion signal operably linked to a heterologous fibrinogen Bβ chain, the DNA segment comprising genomic DNA encoding the Bβ chain; and

a third DNA segment encoding a secretion signal operably linked to a to a [sic] heterologous fibrinogen γ chain, the DNA segment comprising genomic DNA encoding the γ chain, wherein each chain is from the same species, and wherein each of said first, second and third segments is operably linked to additional DNA segments required for its expression in the mammary gland of a host female mammal.